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Communications

Stereospecific Methylation of γ,δ-Epoxy Acrylates by Trimethylaluminum: A Method for the Iterative Construction of Polypropionate Chains

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Summary: A new and potentially useful method for the synthesis of polypropionates via the regio- and stereospecific methylation of γ,δ-epoxy acrylates by $(CH_3)_3Al$ has been developed.

The polypropionate-derived chains found in many macrolide antibiotics consist of characteristic sequences of alternating methyl- and hydroxyl-substituted carbon atoms. Compounds that possess such structural features have elicited much attention from synthetic organic chemists due to the challenges that are encountered in their synthesis.[2] Although much progress toward the synthesis of such compounds has undoubtedly been brought by the judicious use of stereoselective aldol condensations,[2-5] more recent efforts have focused on the use of methods that permit the stereoselective iterative construction of polypropionate-derived chains.[6,7]

We now wish to describe such a method, one that involves the stereospecific methylation of γ,δ-epoxy acrylates by trimethylaluminum ($(CH_3)_3Al$)[8,9] in the presence of water. Furthermore, we demonstrate its usefulness by applying it to the synthesis of some short-chain polypropionates.[10]

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(9) Recently, it was reported that the reaction of methyl 4,5-epoxy-2-hexenoate with methylcopper reagents or trimethylaluminum gave mixtures of four stereoisomeric products, the ratio of which varied. See: Ibuka, T.; Tanaka, M.; Nemoto, H.; Yamamoto, Y. *Tetrahedron* **1989**, *45*, 435.

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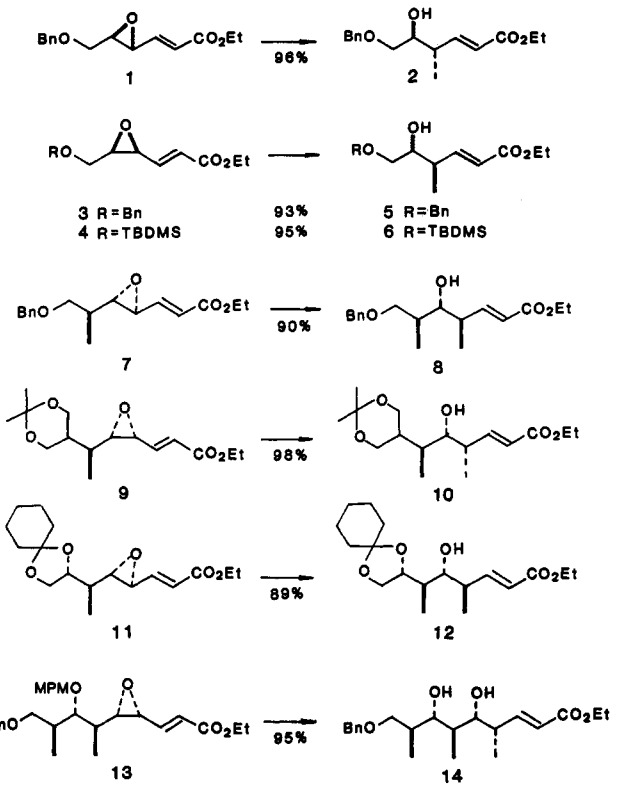
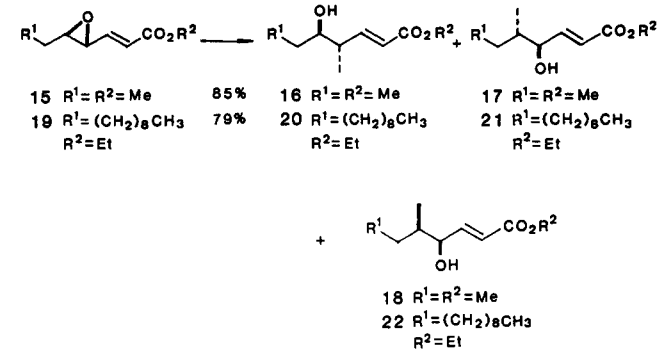
Scheme I[a]



[a] $(CH_3)_3Al$ (2 M hexane solution, 10 equiv), H_2O (6 equiv), $ClCH_2CH_2Cl$, −30 °C, 1–1.5 h.

Thus, treatment of the ethyl 6-(benzyloxy)-4,5-*trans*-epoxy acrylate **1** with $(CH_3)_3Al$ (2 M solution in hexane, 10 equiv) in 1,2-dichloroethane in the presence of water (6 equiv) at −30 °C for 1 h, followed by aqueous workup, gave solely the anti compound **2**, in which a methyl group was stereospecifically introduced at the γ-position with net inversion of configuration, in 96% yield (Scheme I).[11] The isomeric purity of the product, a measure of the diastereoselectivity of the reaction, was found to be greater than 99% by 600-MHz ^1H NMR and HPLC analysis.[12,13] Similarly, the reaction of the analogous *cis*-epoxy acrylates **3** and **4** with $(CH_3)_3Al$ under the same conditions stereospecifically produced the *syn*-compounds **5** (93%) and **6** (95%), respectively, with complete diastereoselectivity.[11-13] Also, an optically active homologue (**8**), which possesses three contiguous chiral centers, i.e., the 4,5-anti-5,6-anti diastereomer, was readily produced from **7**,[14] in 90% yield.[12] Furthermore, the chiral (*Z*)-epoxy acrylate **9**[15] (−30 °C, 1.5 h) furnished solely the 4,5-syn-5,6-anti-compound **10**, in 98% yield.[12] Thus, regardless of the geometry of the epoxy group, methylation of γ,δ-epoxy *trans*-acrylates by $(CH_3)_3Al$ proceeds cleanly and stereospecifically, with net inversion of configuration (Scheme I). On the other hand, attempts to stereospecifically methylate the analogous γ,δ-epoxy-*cis*-acrylates failed.[16]

Scheme II[a]



[a] $(CH_3)_3Al$ (2 M hexane solution, 10 equiv), H_2O (6 equiv), $ClCH_2CH_2Cl$, −30 to −15 °C, 6 h.

In all cases, the best results were obtained when the reaction was performed at −30 °C and used 8 to 10 equiv of $(CH_3)_3Al$ in 1,2-dichloroethane or dichloromethane in the presence of water (6 to 10 equiv).[17] The presence of water is critical[18] because in its absence reaction does not occur to any appreciable extent. Reaction is generally rapid and, at −30 to −40 °C, requires less than 1.5 h to reach completion.

The major feature of the method described here is that methylation occurs stereospecifically and highly diastereoselectively. Consequently anti compounds are produced from (*E*)-epoxy acrylates and syn compounds are produced from (*Z*)-epoxy acrylates, both in excellent yield.[19] In addition, the method can be applied iteratively. For example, the optically active (*E*)-epoxy acrylate **11**, derived from the enantiomer of **2**, gave exclusively (−30 to −15 °C, 1.5 h) compound **12**, in which four contiguous chiral centers are present, in 89% yield (Scheme I).[12,20] Similarly, on treatment of **13** with $(CH_3)_3Al$ (−30 °C, 1 h), a single

(11) The stereochemistry of the product was unambiguously established by NMR (600 MHz) spectroscopic techniques, of which spin decoupling was one.

(12) The crude reaction mixture was carefully analyzed by ^1H NMR (600 MHz). No other stereoisomers were detected.

(13) ^1H NMR spectra ($CDCl_3$ solution) were recorded with a Bruker AM-600 Instrument. We thank Dr. M. Ueno for recording the spectra. **2**: 7.39–7.29 (m, 5 H), 7.00 (dd, 1 H, *J* = 15.8, 8.3 Hz), 5.85 (dd, 1 H, *J* = 15.8, 1.2 Hz), 4.55 (s, 2 H), 4.19 (q, 2 H, *J* = 7.1 Hz), 3.75 (m, 1 H), 3.54 (dd, 1 H, *J* = 9.2, 3.1 Hz), 3.41 (dd, 1 H, *J* = 9.2, 7.6 H), 2.52 (m, 1 H), 2.35 (d, 1 H, *J* = 3.7 Hz, OH), 1.29 (t, 3 H, *J* = 7.1 Hz), 1.10 (d, 1 H, *J* = 6.7 Hz). **5**: 7.38–7.29 (m, 5 H), 6.89 (dd, 1 H, *J* = 15.7, 8.2 H), 5.84 (dd, 1 H, *J* = 15.7, 1.2 Hz), 4.54 (d, 1 H, *J* = 11.8 Hz), 4.53 (d, 1 H, *J* = 11.8 Hz), 4.19 (q, 2 H, *J* = 7.1 Hz), 3.72 (dt, 1 H, *J* = 7.0, 3.1 Hz), 3.52 (dd, 1 H, *J* = 9.5, 3.1 Hz), 3.39 (dd, 1 H, *J* = 9.5, 7.0 Hz), 2.52 (ddq, 1 H, *J* = 7.0, 6.8, 1.2 Hz), 2.41 (br s, 1 H, OH), 1.29 (t, 3 H, *J* = 7.1 Hz), 1.14 (d, 3 H, *J* = 6.8 Hz). **6**: 6.90 (dd, 1 H, *J* = 15.7, 8.3 Hz), 5.85 (dd, 1 H, *J* = 15.7, 1.2 Hz), 4.20 (q, 2 H, *J* = 7.1 Hz), 3.63 (dd, 1 H, *J* = 9.8, 3.1 Hz), 3.54 (m, 1 H), 3.47 (dd, 1 H, *J* = 9.8, 6.7 Hz), 2.49 (m, 1 H), 2.48 (d, 1 H, *J* = 4.3 Hz, OH), 1.29 (t, 3 H, *J* = 7.1 Hz), 1.14 (d, 3 H, *J* = 6.8 Hz).

(14) This compound was prepared by the Horner–Wittig reaction of the aldehyde obtained by the Swern oxidation of (2*S*,3*S*)-5-(benzyloxy)-2,3-epoxy-4-methylpentanol.[5b]

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(16) For example, the reaction of the *cis*-acrylate isomer of **1** with $(CH_3)_3Al$ gave an unstable 5-hydroxy allenic ester (60%), along with a mixture of methylated diastereomers (19%). That such a mixture of products was obtained is presumably a consequence of the conformation preferentially assumed by the *cis*-acrylate. That is, the carbon–carbon double bond may be oriented perpendicular to the carbon–carbon single bond of the epoxy group because of steric repulsion between the ester group and the hydrogen atoms of the epoxide ring.

(17) The use of excess trimethylaluminum was required to drive the reaction to completion. Also, at temperatures below −50 °C, reaction did not take place at any appreciable rate.

(18) The water probably reacts with $(CH_3)_3Al$ to generate species like (i) or (ii) or both. Both species are potent methylating agents. See: Storr, A.; Jones, K.; Laubengayer, A. W. *J. Am. Chem. Soc.* **1968**, *90*, 3173. Harney, D. W.; Meisters, A.; Mole, T.; *Aust. J. Chem.* **1974**, *27*, 1639. When methanol was used in place of water, no reaction occurred and the starting material was recovered.

$(CH_3)_2AlOAl(CH_3)_2$ (i) $\quad CH_3AlO$ (ii)

(19) The stereoselective synthesis of syn and anti isomers of homoallylic alcohols via the Pd-catalyzed hydrogenolysis of alkenyloxiranes, among which were some γ,δ-epoxy-γ-methyl acrylates, was recently described. In contrast to the method described here, *trans*-epoxy acrylates gave syn isomers whereas *cis*-epoxy acrylates afforded anti isomers. See: Oshima, M.; Yamazaki, H.; Shimizu, I.; Nisar, M.; Tsuji, J. *J. Am. Chem. Soc.* **1989**, *111*, 6280.

(20) For the synthesis of diastereomers with four contiguous chiral centers, see ref 5g.

product, the expected product, **14**, in which five contiguous chiral centers are present, was obtained in 95% yield.[21]

We also examined the reaction of substrates that bear no ether oxygen atom at the ϵ or ζ position (Scheme II).[9] Such compounds reacted much more slowly than epoxy acrylates, which bear an ether oxygen atom at the ϵ or ζ position (e.g., **1**, **3**, **4**, **7**, **9**, **11**, and **13**) and gave mixtures of regioisomeric products. For example, the reaction of methyl (4*R*,5*R*)-4,5-epoxy-2-heptenoate (**15**) with $(CH_3)_3Al$ required more than 6 h at −15 to −10 °C to go to completion and gave an 80:18:2 mixture of **16**, **17**, and **18**, in 85% combined yield.[9] Similarly, the reaction of ethyl 4,5-epoxy-2-pentadecenoate (**19**) (−15 to −10 °C, 6 h) gave a 78:21:1 mixture of **20**, **21**, and **22** in 79% yield. The results suggest that chelation of the aluminum reagent by the oxygen atoms of the epoxide and the ether moiety at the ϵ or ζ position is important for the achievement of extremely high regioselectivity, as is seen in the reactions of **1**, **3**, **4**, **7**, **9**, **11**, and **13**.[8]

The results of further studies of the methylation reaction and the application of the methodology described here to the synthesis of natural products will be reported shortly.

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(21) The MPM protective group was concomitantly removed under the conditions.

On the Stereoselective Opening of Chiral Dioxane Acetals. Nucleophile Dependence

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Summary: The stereoselective allylation of chiral dioxane acetals **1** was found to be highly dependent on the nature of allylmetal reagent in the following order: Ph_3Si (19/1) < Me_3Si (58/1) < Ph_3Sn (90/1) < Me_3Ge (100/1) < *n*-Bu_3Sn (>300/1). The allylation with allyltributylstannane was significantly more selective than allyltrimethylsilane for a number of chiral dioxane acetals examined.

The Lewis acid assisted, nucleophilic opening of chiral acetals has evolved into a powerful method for the stereoselective formation of carbon-carbon bonds,[1] Scheme I. Of the many reagents capable of participating in this reaction, silicon-containing nucleophiles (allylsilanes, propargylsilanes, silylacetylenes, enol silyl ethers, ketene silyl acetals, TMS cyanide) have proven most versatile. In a recently completed study on the mechanism of reaction of dioxane acetals with allyltrimethylsilane, we demonstrated the importance of substrate structure and experimental conditions (Lewis acid, solvent, stoichiometry, concentration, temperature) on the stereochemical outcome.[2] *We report herein that the nucleophilicity of the allylating reagent also has a significant impact on the stereoselectivity of reaction.*

The optimized procedure described by Johnson[3] for the allylation of chiral acetals **1** involves the use of 8 equiv of allyltrimethylsilane and 11 equiv of a 6/5 blend of $TiCl_4$/Ti(O-*i*-Pr)$_4$. By following the recommended slow addition (2 h, syringe pump) of the Lewis acid we were able to reproduce the reported selectivities. Thus, using this standardized protocol for reaction with the *n*-hexyl acetal (±)-**1a** we surveyed five allylating agents bearing different metals and groups on the metal, Table I. Two important trends are apparent from these data. First, for similar R groups the trend Si < Ge < Sn is seen (compare entries 1, 3, 4 and 2, 5). Second, for a given metal, phenyl groups attenuate the selectivity compared to alkyl groups (compare 1 and 2, 4 and 5).

Scheme I

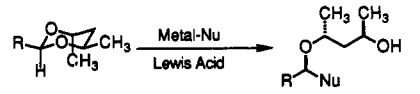
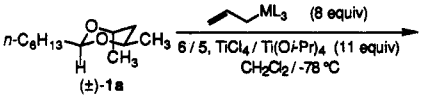
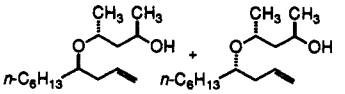


Table I. Allylation of (±)-1a: Nucleophile Dependence[a]





(*lk*)-**2a** (*ul*)-**2a**

entry	L_3M (equiv)	time[b] (h)	yield[c] (%)	*lk*/*ul*-**2a**	$\Delta\Delta G^{\ddagger}$[d]
1	Me_3Si (8)	3	100	58/1	1.58
2	Ph_3Si (8)	6	80	10/1	1.14
3	Me_3Ge (8)	3	100	100/1	1.79
4	*n*-Bu_3Sn (8)	3	100	270/1	2.17
5	Ph_3Sn (8)	3	100	90/1	1.75

[a] All reactions performed with 11 equiv of a 6/5, $TiCl_4$/Ti(O-*i*-Pr)$_4$ blend 0.2 M in CH_2Cl_2. [b] Total reaction time. [c] All yields and ratios based on response factors versus cyclododecane. [d] At 195 K, kcal/mol.

Table II. Allylation of (±)-1a with Allyltributylstannane: Stoichiometry Effects[a]

entry	Lewis acid[b] (equiv)	stannane (equiv)	yield[c] (%)	*lk*/*ul*-**2a**[c]	$\Delta\Delta G^{\ddagger}$[d]
1	6/5	8	100	270/1	2.17
2	6/5	1	97	300/1	2.21
3	5/5	1	100	>300/1	>2.21
4[e]	5/5	1	93[f]	568/1	2.40
5	2.5/2.5[g]	1	32		
6	2.5/2.5[g]	2	55	>230/1	>2.11

[a] All reactions run in CH_2Cl_2 (0.1 M) at −78 °C. [b] $TiCl_4$/Ti(O-*i*-Pr)$_4$ (0.2 M in CH_2Cl_2) added by syringe pump over 2 h. [c] Based on response factors versus cyclododecane. [d] At 195 K (kcal/mol). [e] 2.5 mmol scale. [f] Yield of isolated, purified product. [g] Added over 1 h.

While these trends have clear mechanistic significance (vide infra), the dramatic improvement in selectivity for

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